American Journal of Medical Genetics 63:447–453 (1996)

CVS-Exposed Limb Deficiency Defects With or Without Other Birth Defects: Presentation of Six Cases Born During a Period of Nine Years

Chih-Ping Chen, Fen-Fen Liu, Sheau-Wen Jan, Shuan-Pei Lin, and Chung-Chi Lan

Departments of Obstetrics and Gynecology (C.-P.C., C.-C.L.), Pediatrics (S.-P.L.), and Medical Research (C.-P.C., S.-P.L., F.-F.L., S.-W.J.), Mackay Memorial Hospital, Taipei, Taiwan, Republic of China

We report on six cases with CVS-exposed limb-"reduction" defects born in our hospital during a period of 9 years (1986–1994). Four cases were associated with other birth defects. One had an oromandibular-limb hypogenesis syndrome with a cleft lip and jejunal atresia, a second had an oromandibular-limb hypogenesis (Hanhart) syndrome, a third had severe flexion deformity at the hips and hyperextension at the knees with meconium peritonitis and intestinal obstruction, and a fourth had Poland anomaly. Detailed clinical descriptions, prenatal diagnosis, photographs, and radiographs are presented. Our presentation adds to the information on severe limb abnormalities after CVS and suggests CVS-exposed limb defects may be associated with other birth defects resulting from vascular insufficency or intrauterine compression. We suggest that detailed post-CVS sonographic follow-ups are necessary for each CVS-exposed case to identify not only the possible fetal limb reduction, but also vascular disruption-type malformations and compressive deformities.

KEY WORDS: **chorionic villus sampling, limb defect, malformation, deformation, prenatal diagnosis**

INTRODUCTION

Chorionic villus sampling (CVS) affords the advantage of early prenatal diagnosis of fetal genetic disorders for women having appropriate indications. However, in Taiwan, this procedure had also been in widespread use to determine fetal sex until 1993 when legal prohibition of the improper use of CVS for fetal gender identification ensued. Infants born with limb defects after CVS have occasionally been reported. We reviewed all the cases of limb defects occurring at Mackay Memorial Hospital, Taipei, Taiwan over a period of 9 years (1986–1994). The prenatal diagnosis, postnatal findings, perinatal outcome, and the associated birth defects of the six cases following chorionic villus sampling are reported.

Received for publication June 23, 1995; revision received September 8, 1995.

Address reprint requests to Dr. Chih-Ping Chen, Departments of Obstetrics and Gynecology, and Medical Research, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan, Republic of China.

METHODS

During a 9-year period (1986–1994), among 64,432 consecutive live and stillbirths delivered at Mackay Memorial Hospital, Taipei, Taiwan, 30 pregnancies complicated by fetal limb defects were identified and reviewed. Six cases had a history of CVS exposure during early pregnancy. Among the other 24 CVS-unexposed infants, 6 had amniotic band sequence with characteristic malformations of various limb amputations by constrictive bands, encephaloceles, facial clefts and abdominal wall defects, and 18 had natural limb defects without other birth defects. We collected detailed data of six CVS-exposed infants including maternal history, prenatal sonograms, associated birth defects, birth weight, birth gestational age, and the procedure, instrument and timing of the CVS. These cases did not have the following conditions during the course of pregnancy: maternal exposure to teratogenic agents, vascular disruptive agents or irradiation, familiy history of limb defect, maternal diabetes, infectious diseases of cytomegalovirus and herpes, uterine malformations or tumors, and consanguinity.

A summary of the clinical data and distribution of limb abnormalities and associated birth defects is given in Table I, and a comparison of the prevalence of all types of limb deficiencies and other defects between CVS-exposed and CVS-unexposed infants (excluding cases with amniotic band syndrome) is given in Table II.

CLINICAL REPORTS

Case 1

Case 1 was a 31-year-old gravida 4, para 3 woman, who came to our hospital for prenatal care at 33 weeks

TABLE I. Fetal Limb Anomalies and Associated Birth Defects in 6 Patients Who Had Previously Undergone Chorionic Villus Sampling*

Case no.	Indication	Maternal age (years)	Gestational weeks	Karyotype	Procedure	Limb defects	Associated birth defects
1	Gender identification	31	8	46,XY	TC	Partial absence of both hands, digital deficiencies of all digits with existence of the vestiges of the digits; complete absence of the left foot and five toes	Oromandibular-limb hypogenesis anomaly (microglossia; micrognathia); a cleft lip; jejunal atresia
2	Gender identification	28	10	46,XY	TC	Complete absence of the right forearm, right hand and five digits, partial absence of the left leg; complete absence of both feet and all toes	Oromandibular-limb hypogenesis anomaly (microglossia; micrognathia)
3	Gender identification	30	8	46,XY	TC	Partial absence of the right forearm and complete absence of right hand and five digits	No
4	Gender identification	31	8	46,XY	TC	Digital deficiencies of all digits of the right hand; digital deficiencies of digits II, III, and the thumb of the left hand; complete absence of both feet and all toes	No
5	Advanced maternal age	35	7	46,XX	TC	Digital deficiencies of all digits of the left hand; digital deficiencies of digits III, IV, and V of the right hand	Intestinal obstruction with meconium peritonitis; flexion deformity at the hips and hyperextension at the knees
6	Gender identification	33	9	46,XY	TC	Complete absence of digits II, III, IV and V of the right hand with existence of the vestige of the thumb	Poland syndrome (aplasia of the right pectoralis major muscle and pectoralis minor muscle)

*TC: transcervical chorionic villus sampling using Trophocan catheter (Concord/Portex, Keene, N.H.) with 1.13 mm inner diameter and 1.45 mm outer diameter.

TABLE II. The Prevalence of All Types of Limb Deficiencies and Other Birth Defects in CVS-Exposed and CVS-Unexposed Limb Defects*

	Infants with limb defects		
	CVS-exposed	[a]CVS-unexposed	P
Limb deficiencies			
transverse limb defect of the long bone (partial absence of the long bone)	2 (33.3%)	0	<0.01
longitudinal limb defect of the long bone (complete absence of the long bone)	1 (16.7%)	2 (11.1%)	>0.1
terminal transverse limb defect (complete absence of the hand or foot but existence of the long bone)	3 (50.0%)	1 (5.6%)	<0.01
terminal longitudinal limb defect (absence or deficiency of the digit but partial existence of the hand or foot)	4 (66.7%)	15 (83.3%)	>0.1
Other birth defects	4 (66.7%)	0	<0.01
Total cases	6	18	

*Note: several defects may be present in one case.
[a]Exclusion of cases with amniotic band syndrome.

of gestation. Sonographic examination showed polyhydramnios with intestinal obstruction. She underwent transcervical CVS with the Trophocan catheter (Concord / Portex, Keene, N.H) at 8 weeks of gestation at a private clinic for gender identification and the karyotype was found to be 46,XY. The mother underwent cesarean section at 38 weeks of gestation due to a previous cesarean section. A male infant weighing 3,356 gm was born with absence of the left foot, oromandibular-limb hypogenesis (Hanhart) anomaly, a cleft lip, partial absence of both hands, deficiencies of all digits, existence of vestiges of the digits, microglossia, micrognathia, and jejunal atresia (Fig. 1). He died of intestinal obstruction and respiratory failure 2 weeks after birth.

Case 2

Case 2 was a 28-year-old gravida 5, para 2 woman, who came to our hospital for prenatal care at 30 weeks of gestation. Sonographic examination showed a normal male fetus. She underwent transcervical CVS with the Trophocan catheter at 10 weeks of gestation at a private clinic for gender identification and the karyotype was found to be 46,XY. A male infant weighing 3,032 g was born by vaginal delivery at 41 weeks of gestation with microglossia and micrognathia, oromandibular-limb hypogenesis anomaly, absence of the right forearm, right hand and five digits, partial absence of the left leg, and absence of both feet (Fig. 2). The infant was discharged in a good condition.

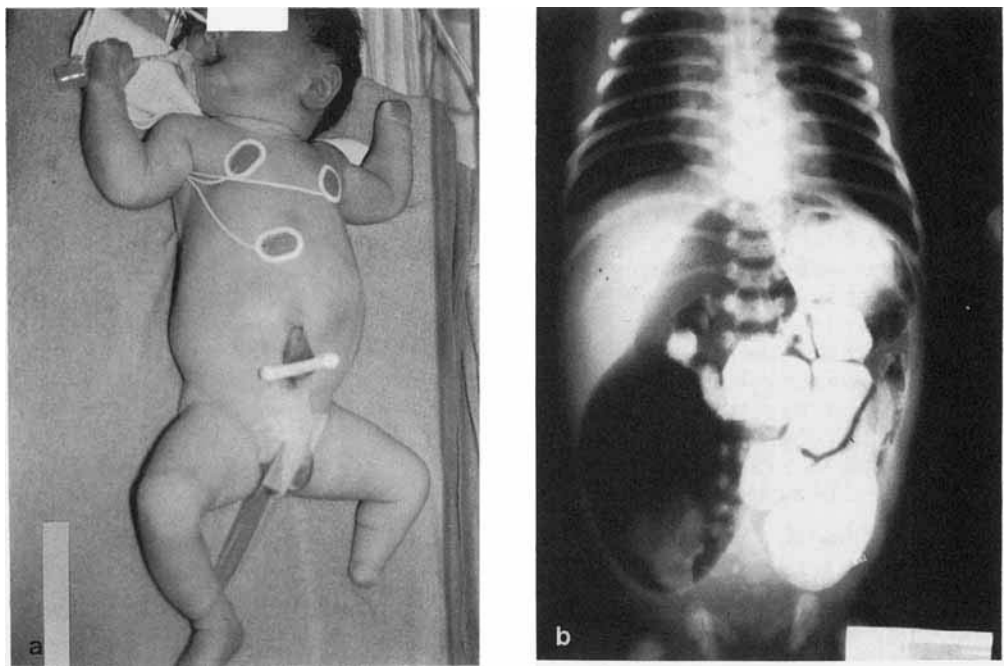

Fig. 1. Case 1: (**a**) oromandibular-limb hypogenesis anomaly with cleft lip; (**b**) radiograph of the intestine showing jejunal atresia.

Fig. 2. Case 2: oromandibular-limb hypogenesis anomaly.

Fig. 3. Case 3: right upper limb.

Case 3

Case 3 was a 30-year-old gravida 2, para 1 woman, who came to our hospital for prenatal care at 14 weeks of gestation. Sonographic examination documented a normal fetus. She underwent transcervical CVS with the Trophocan catheter at 8 weeks of gestation at a private clinic for gender identification and the karyotype was found to be 46,XY. The mother underwent cesarean section at 38 weeks of gestation due to a previous cesarean section. A male infant weighing 3,420 g was born with partial absence of the right forearm and absence of the right hand (Fig. 3). The infant was discharged in a good condition.

Case 4

Case 4 was a 31-year-old gravida 4, para 2 woman, who came to our hospital for prenatal care. No sonographic examination was performed during her prenatal visits. She underwent transcervical CVS with the Trophocan catheter at 8 weeks of gestation at a private clinic for gender identification and the karyotype was found to be 46,XY. A boy weighing 3,300 g was delivered vaginally at 40 weeks of gestation with absence of both feet digital deficiencies of all digits of the right hand and of digits II, III, and the thumb of the left hand (Fig. 4). The infant was discharged in a good condition.

Case 5

Case 5 was a 35-year-old primigravida 1 woman, who came to our hospital for prenatal care at 38 weeks of gestation. A sonographic examination demonstrated intestinal obstruction with peritoneal calcification and meconium peritonitis (Fig. 5). She underwent transcervical CVS with a Trophocan catheter at 7 weeks of gestation at a private clinic due to advanced maternal age and the karyotype was found to be 46,XX. The mother underwent cesarean section at 39 weeks of gestation due to primibreech. A girl weighing 2,660 g was born with flexion deformity at the hips and hyperextension at the knees, digital deficiencies of all digits of the left hand and of digits III, IV, and V of the right hand (Fig.

Fig. 4. Case 4: four limbs.

Fig. 5. Case 5: prenatal ultrasound showing intestinal obstruction and meconium peritonitis with calcified spots (arrow).

6), and intestinal obstruction with meconium peritonitis. The infant died of sepsis 3 weeks after birth.

Case 6

Case 6 was a 33-year-old gravida 3, para 2 woman, who came to our hospital for prenatal care. No sonographic examination was performed during her prenatal visits. She underwent transcervical CVS with the Trophocan catheter at 9 weeks of gestation at a private clinic for gender identification and the karyotype was found to be 46,XY. A boy weighing 3,462 g was delivered vaginally at 40 weeks of gestation with absence of digits II, III, IV and V of the right hand with existence of the vestige of the thumb, aplasia of the right pectoralis major muscle and pectoralis minor muscle, which are compatible with the clinical manifestations of Poland anomaly (Figs. 7, 8). The infant was discharged in a good condition.

Fig. 6. Case 5: four limbs.

DISCUSSION

The timing of CVS performance and experience of the operators play important roles in CVS-exposed limb reduction defects. GIDEF [1993] suggested that CVS should not be performed at less than 10 weeks' gestation unless additional evidence is obtained. Our 6 cases of CVS-exposed limb defects had undergone transcervical CVS performed by less-experienced practitioners at private clinics between 56 to 70 days of gestation, mostly for the purpose of gender identification. However, no such CVS-exposed limb defects or associated malformations were found among 67 transcervical CVS and 1,240 transabdominal CVS performed by experienced physicians at our hospital during the study period. Our case 1 and case 6 had been listed as case 14 and case 20, respectively, in the series of Hsieh et al. [1995]. Hsieh et al. [1995] surveyed the causal relationship between CVS and limb defects in Taiwan during 1991 and found a higher incidence of limb defects after CVS (0.294%) compared with that of natural limb defects (0.032%), and a higher incidence of severe limb defects with CVS exposure (0.22%) compared with that in the general population (0.0026%). In their series, operators' inexperience and multiple CVS samplings contributed to the increased incidence and the severity of limb defects. In our series, the prevalence of severe limb defects and other associated birth defects was also increased in CVS-exposed infants.

Hoyme et al. [1982] developed the concept of vascular pathogenesis of fetal transverse limb deficiencies. Brent [1990] suggested that the mechanism of fetal limb defects can be a form of intrauterine vascular insult leading to hypoperfusion of the fetus. D'Alton [1994] suggested that the disruption of the vessels supplying the extracorporeal fetal circulation caused by

Fig. 7. Case 6: Poland anomaly.

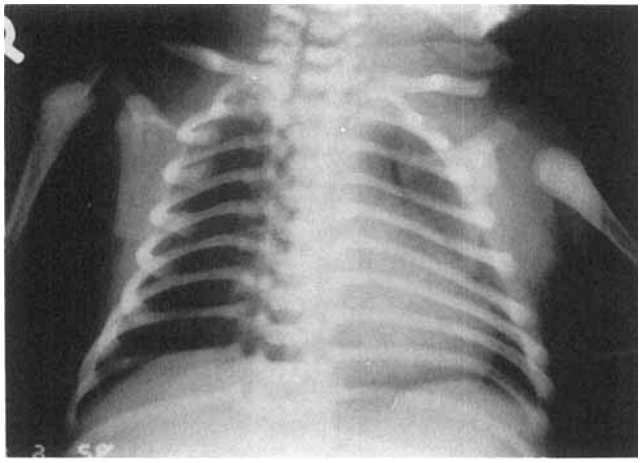

Fig. 8. Case 6: radiograph of thorax showing asymmetry of the thoracic cage due to aplasia of the right pectoralis major and the minor muscles.

CVS can likewise result in the release of vasoactive peptides and produce fetal vasospasm and hypoperfusion of the fetal circulation. Oromandibular-limb hypogenesis complex (cases 1 and 2) has been considered to have a pathogenetic mechanism such as hypoperfusion [Flannery, 1990; Firth et al., 1991b]. Firth et al. [1991a] first reported on five infants born to women who had undergone CVS in early pregnancy. In their study, four had oromandibular-limb hypogenesis syndrome and the fifth had a terminal limb defect. All the cases of limb defects had followed transabdominal CVS performed between 55 to 66 days of gestation. A report from the National Institute of Child Health and Human Development (NICHD) workshop on chorionic villus sampling and limb and other defects demonstrated that the oromandibular-limb hypogenesis complex is common among CVS-exposed infants [Report of the NICHD workshop, 1993]. Other birth defects reported so far in CVS-exposed infants included hemangiomas [Burton et al., 1995]; a central cleft lip [Mastroiacovo et al., 1992]; a cleft of soft palate [Firth et al., 1991a]; Möbius syndrome [Firth et al., 1991a]; a cleft lip with or without cleft palate, a nasal encephalocele, a large port-wine stain, craniosynostosis, an omphalocele, ambiguous genitals and undescended testes [Burton et al., 1992]; a horseshoe kidney, diaphragmatic hernia, imperforate anus and absent vagina [Report of the NICHD workshop, 1993]; a porencephalic cyst [Fabris et al., 1992]; and a congenital scalp defect, hydrocephaly, congenital heart defects, myelomeningocele, cataract, a pulmonary cyst, pyloric stenosis, syndactyly, hypospadias, malformations of the kidney, omphalocele, hemangioma, talipes equinovarus and dislocation of the hip [GIDEF, 1993].

Jejunal atresia (case 1) has been produced experimentally in dogs by occlusion of branches of the superior mesenteric artery, as a consequence of the intestinal ischemia in utero [Louw, 1966]. Meconium perotonitis (case 5) can result from vascular impairment, and occlusion and thrombosis of the mesenteric arteries are frequently demonstrated on pathologic examination in cases of meconium peritonitis [Forouhar, 1982; Tibboel et al., 1986]. In the Poland anomaly (case 6), Bouvet et al. [1976] have presented evidence of diminished blood flow to the affected side, and have suggested that the primary defect may be in the proximal subclavian artery with early deficit of blood flow to the distal limb and pectoral region. Bavinck and Weaver [1986] postulated that Poland syndrome and Möbius syndrome were caused by interruption of early embryonic blood in the subclavian arteries, the vertebral arteries, or their branches. An increase in the prevalence of vascular disruption-type malformations (congenital amputation of the non-symmetrical type, orofacial malformations such as mandibular hypoplasia, cleft palate and Möbius syndrome) has been observed in CVS-exposed infants [Report of the NICHD workshop, 1993; Brent, 1993]. However, Shepard et al. [1991] suggested that inadvertent amniotic puncture during CVS can result in either amniotic bands or loss of amniotic fluid with subsequent compressive deformities. They also suggested the possibility of entrapment of distal limbs in the exocoelomic gel, resulting in transient immobilization with subsequent ischemia and necrosis. Flexion deformity at the hips and hyperextension at the knees (case 5) result from intrauterine compression and are possibly due to loss of amniotic fluid in early pregnancy by inadvertent amniotic puncture during CVS. Amniotic band syndrome, oligohydramnios, vascular compression, thrombosis, embolization, maternal diabetes, maternal infections (cytomegalovirus and herpes), vascular disruptive agents, including vasoconstrictive drugs, such as cocaine and vasodilatative drugs (nifedipine, nitrendipine, felodipine and hydrazine), consanguinity, and familial predisposition have all been shown to cause limb malformation [Hoyme et al., 1982; Brent, 1990; Danielsson et al., 1990; Jones, 1991; van den Anker et al., 1993]. Those factors, although not occurring in our series, should all be considered when evaluating CVS-exposed limb defects and associated birth defects.

Our presentation suggests CVS-exposed limb defects may be associated with other birth defects resulting from vascular insufficiency or intrauterine compression. Therefore, detailed post-CVS sonographic follow-ups are necessary for each CVS-exposed case to identify not only the possible fetal limb defects but also the vascular disruption type malformations and compressive deformities.

REFERENCES

Bavinck JNB, Weaver DD (1986): Subclavian artery supply disruption sequence: Hypothesis of a vascular etiology for Poland, Klippel-Feil, and Möbius anomalies. Am J Med Genet 23:903–918.

Bouvet J, Maroteaux P, Briad-Guillemot M (1976): Poland's syndrome: Clinical and genetic studies-physiopathology. Nouv Presse Med 5:185.

Brent RL (1990): Relationship between uterine vascular clamping, vascular disruption syndrome and cocaine teratology. Teratology 41:757–760.

Brent RL (1993): What is the relationship between birth defects and pregnancy bleeding? New perspectives provided by the NICHD workshop dealing with the association of chorionic villous sampling and the occurrence of limb reduction defects. Teratology 48:93–95.

Burton BK, Schulz CJ, Burd LI (1992): Limb anomalies associated with chorionic villus sampling. Obstet Gynecol 79:726-730.

Burton BK, Schulz CJ, Angle B, Burd LI (1995): An increased incidence of haemangiomas in infants born following chorionic villus sampling (CVS). Prenat Diagn 15:209–214.

D'Alton ME (1994): Prenatal diagnostic procedures. Semin Perinatol 18:140–162.

Danielsson BRG, Danielson M, Reiland S, Rundqvist E, Dencker L, Regard CG (1990): Histological and in vitro studies supporting decreased uteroplacental blood flow as explanation for digital defects after administration of vasodilators. Teratology 41:185- 193.

Fabris C, Licata D, Garzena E, Gandione M, Mostert M (1992): Porencephalic cyst after chorionic villus sampling. Prenat Diagn 12:1074.

Firth HV, Boyd PA, Chamberlain PF, MacKenzie IZ, Lindenbaum RH, Huson SM (1991a): Severe limb abnormalities after chorion villus sampling at 56–66 days'gestation. Lancet 337:762–763.

Firth HV, Boyd PA, Chamberlain PF, MacKenzie IZ, Lindenbaum RH, Huson SM (1991b): Limb abnormalities and chorion villus sampling. Lancet 338:51.

Flannery DB (1990): Hypoglossia-hypodactylia. In Buyse ML (ed): "Birth Defects Encyclopedia." Dover: Center For Birth Defects Information Services, Inc., pp 920–921.

Forouhar F (1982): Meconium peritonitis: Pathology, evolution, and diagnosis. Am J Clin Pathol 78:208–213.

GIDEF–Gruppo Italiano Diagnosi Embrio-Fetali: Mastroiacovo P, Tozzi AE, Agosti S, Bocchino G, Bovicelli L, Dalpra L, Carbone LD, Lituania M, Luttichau A, Mantegazza F, et al. (1993): Transverse limb reduction defects after chorion villus sampling: A retrospective cohort study. Prenat Diagn 13:1051–1056.

Hoyme HE, Jones KL, van Allen MI, Staunders BS, Benirschke K (1982): Vascular pathogenesis of transverse limb reduction defects. J Pediatr 101:839–843.

Hsieh FJ, Shyu MK, Sheu BC, Lin SP, Chen CP, Huang FY (1995): Limb defects after chorionic villus sampling. Obstet Gynecol 85:84–88.

Jones KL (1991): Developmental pathogenesis of defects associated with prenatal cocaine exposure: Fetal vascular disruption. Clin Perinatol 18:139–146.

Louw JH (1966): Jejunoileal atresia and stenosis. J Pediatr Surg 1: 8–23.

Mastroiacovo P, Botto LD, Cavalcanti DP, Lalatta F, Selicorni A, Tozzi AE, Baronciani D, Cigolotti AC, Giordano S, Petroni F, Puppin F (1992): Limb anomalies following chorionic villus sampling: A registry based case-control study. Am J Med Genet 44:856–864.

Report of national institute of child health and human development (NICHD) workshop (1993) on chorionic villus sampling and limb and other defects, October 20, 1992. Am J Obstet Gynecol 169:1–6; Teratology 48:7–13.

Shepard TH, Kapu RP, Fantel AG (1991): Limb-reduction defects and chorion villus sampling [letter]. Lancet 337:1092.

Tibboel D, Gaillard JLJ, Molennaar JC (1986): Importance of mesenteric vascular insufficiency in meconium peritonitis. Hum Pathol 17:411–416.

van den Anker J, Vught EE, Zandwijken GRJ, Cohen-Overbeek TE, Lindhout D (1993): Severe limb abnormalities: analysis of a cluster of five cases born during a period of 45 days. Am J Med Genet 45:659–667.